CLINICAL CONFERENCE

FROM THE MEDICAL STAFF CONFERENCE OF THE UNIVERSITY OF CALIFORNIA HOSPITAL, SAN FRANCISCO, MARCH 19, 1947

CASE PRESENTATION BY DR. GOFMAN:* The patient is a 31 year old married housewife who entered the hospital on February 21 with fever, abdominal pain and tenderness of 30 hours' duration. The present illness began two years ago when she first noted transient ankle edema at the end of the day for periods of two or three days at a time. During the year before her entry she noticed a generalized loss of energy. In October of last year she had all of her upper teeth extracted. Following this there was drainage of yellow pus from her gums for three weeks, associated with swelling and tenderness of the gums. In December the gums were scraped by her dentist with apparent healing. On January first, she awoke to find herself swollen throughout. Her eyes were swollen shut; there was edema of the hands and of the legs, and swelling of the abdomen. She was treated throughout the month of January by her local physician with thyroid extract three grains a day, vitamins, and mercurial diuretics, without improvement. On February 20, after having had the edema for about a month and a half, she noted pain in the lower left quadrant followed by the development of a red rash over the entire umbilical region of the abdomen, associated with a couple of shaking chills and fever. She was then advised to come into U. C. Hospital and did so 30 hours after the development of rash, abdominal pain and fever.

Her past history includes scarlet fever at the age of 12 without known complications. At age 20 she had her only pregnancy, during which time no hypertension, albuminuria, or edema was noted.

On entry the temperature was 37.0° C. There were generalized edema and erythematous lesions over the entire lower half of the abdomen and the upper part of the left thigh. The rash was painful and quite tender to palpation. The diagnosis of erysipelas was made. Penicillin was given, 50,000 units every three hours. Within two days the temperature had come down to normal and the pain and redness had disappeared.

The major laboratory findings on entry were as follows: The NPN was 36. (normal). The blood CO_2 and chloride were definitely low. The serum proteins were down to 4.05 grams per 100 cc. with a reversal of the albumin-globulin ratio. The serum sodium was low. The serum calcium was 7.8 grams per 100 cc.; the phosphorous 5.4 grams per 100 cc. Subsequently the CO_2 and chloride showed no significant rise. The proteins remained in the neighborhood of 4 to 5, with a low albumin. The serum potassium was 2 millequivalents per liter. Potassium chloride was given, 6 grams a day, without any essential change in the serum potassium or sodium. After several days of therapy the cholesterol was 444 mgm. per 100 cc. and the serum was obviously milky. A 24 hour urine specimen revealed a protein output of 30 grams. The 24 hour sodium chloride output was 1.5 grams. Routine urinalyses showed occasional granular casts, a few red cells and white cells. Maximum concentration was 1.026. The hemoglobin was high, (15 to 16 grams) before therapy. On the tenth of March, a course of concentrated salt-poor albumin was started, 50 grams a day being given intravenously. After two days of this therapy the edema decreased visibly, the hemoglobin was back up to 14.5 grams. The patient had anorexia throughout the hospital stay, plus some nausea and vomiting. The approximate dietary protein intake was 20 grams a day. The weight she had maintained for the last couple of years had been around 53 kilograms. When she came in it was 62 kg. With some spontaneous diuresis it dropped to 59.5 kg. At the end of the administration of 300 grams of salt-poor albumin, it was 54.5 kg.

DR. JAMES HOPPER, JR.:† I would like to call attention to a few significant symptoms. . . . (Patient was brought in.) Can you tell us how long you have been bedridden?

PATIENT: Since the tenth of January.

DR. HOPPER: Why can't you get up?

PATIENT: Because I get dizzy, and weak and my ears start ringing.

DR. HOPPER: I think these symptoms are very significant, and later we shall try to demonstrate to you that they are dependent upon changes in blood and plasma volume. Another symptom worthy of note is the anorexia. This greatly complicates her treatment which, in part, is one of maintaining protein nutrition.

DR. LESLIE L. BENNETT:‡ This patient presents a typical picture of chronic glomerulonephritis in the nephrotic stage. The diagnosis of glomerulonephritis as opposed to nephrosis is established by the presence of red blood cells and red cell casts in the urine. It is important for the students to remember that chronic glomerulonephritis may be present itself in a variety of clinical forms. The clinical picture may be dominated by hypertension with its attendant cardiac enlargement, hypertensive encephalopathy, or congestive heart failure. Uremia and uremic symptoms may be predominant. Or we may see the chief physiological disturbance to be the albuminuria with its attendant reduction of the plasma protein and

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consequent edema. This patient is a pretty typical example of this last type. She has no hypertension and little evidence of renal failure, but she has marked albuminuria, plasma protein depletion, and edema.

There has been some question in this patient as to whether the low plasma sodium reflects inability of the decreased kidney to conserve sodium, resulting in the depletion of plasma chlorides and bicarbonate as well. I do not believe that this is the case. We know that at the pH of normal blood the plasma proteins are present largely as anions and require the presence of about 18 milliequivalents per liter of sodium ion to maintain electroneutrality. Therefore a reduction of the plasma proteins must as necessity be accompanied by a reduction of plasma fixed base. In the present case the reduction of plasma sodium is almost exactly that predictable from the reduction of the plasma protein. Another way of looking at the same phenomenon is to remember that as the plasma proteins are reduced the electrolytic composition of the plasma must approach that of the interstitial fluid, which normally contains less sodium than does the plasma.

From a therapeutic point of view the immediate goal of treatment is two fold: first, the relief of the edema, which is the origin of the subjective symptoms, and second, the restoration of the depleted plasma protein. Because of her anorexia she has presented a great practical problem in this regard. As was shown, her average dietary intake of protein has been around 20 gm. per day while her urinary output of albumin has been around 30 gm. per day. Thus, she had a negative nitrogen balance during most of her hospital stay and it is not surprising that she showed little improvement. The use of salt free concentrated human albumin is perfectly rational, and it has been an effective diuretic agent. However, the effect of the albumin has not been permanent, and if she does not receive it the edema again increases in severity within 48 hours. I would be inclined to think that the ultimate prognosis for this patient is poor because of the degree of albuminuria and its duration, the evidence suggestive of renal failure, and her failure to respond to anything except concentrated albumin which itself has only palliative results.

DR. HOPPER: I am going to ask Dr. Mudrick to review the blood volume studies for you, since he did the work.

DR. CHARLES J. MUDRICK:* Summarized in the chart are figures relating to blood and plasma volume fluctuations in response to albumin therapy. We have correlated; (1) changes in serum protein concentration and (2) total or absolute amount of circulating serum proteins, (3) packed cell volume, and (4) albumin intake and urinary wastage of protein with the blood volume fluctuations.

When this patient first came in, her total serum proteins were 4.1 grams per 100 cc. Shortly thereafter her PCV was 44. The next few days it was noted the hemoglobin was rising up to about 116 per cent. At this time, February 27, we found that her total blood volume was 3,300 cc., and the red cell volume was 1,550 cc. Serum proteins determined by the falling drop method were 4.4 grams per 100 cc. Knowing the total blood volume, we were able to calculate the total circulating protein, which was 77 grams. In the next few days the packed cell volume and the hemoglobin continued to increase. The final blood volume before giving albumin, was decreased to 2,960 cc. This is definitely below normal for a female with her ideal weight of 55 kilos, and explains partly why, on arising, she felt dizzy and weak. It

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Table Showing Effect of Salt-free Albumin on Blood Volume of Patient in Nephrotic Stage of Glomerulonephritis

Date	Salt-Free Albumin Given	Total Blood Volume in cc.		Plasma Volume in cc.	RBC Volume in cc.	Packed Cell Volume	Total Serum Proteins in Grams per 100 cc. of Blood	Total Circulating Proteins in Grams	Total Urinary Proteins in Grams per 24 Hours
2-24-47	.....	.....	.....	.....	.....	44.0	.....	.....	35.9
2-27-47	.....	3300	60 cc/kilo	1750	1550	46.9	4.40	77.0	.....
2-28-47	.....	.....	.....	.....	.....	50.0	4.79	.....	23.8
3-10-47	50 gm.	2960	54 cc/kilo	1413	1545	52.1	3.28	46.3	28.0
3-11-47	50 gm.	.....	.....	.....	.....	.....	.....	.....	20.0
3-12-47	50 gm.	"3270"	59.3 cc/kilo	"1720"	"1550"	47.2	3.66	"63.0"	19.0
3-13-47	50 gm.								
	Before Albumin	"3300"	59.3 cc/kilo	"1750"	"1550"	46.8	3.66	"64.0"	30.8
	After Albumin	"4220"	76.5 cc/kilo	"2660"	"1550"	36.7	4.29	"114.0"	.....
3-14-47	50 gm.								
	Before Albumin	"3210"	58.4 cc/kilo	"1660"	"1550"	48.2	4.08	"68.0"	16.0
	After Albumin	"4220"	76.5 cc/kilo	"2660"	"1550"	36.7	3.77	100.0	.....
3-21-47	50 gm.								
	After Albumin	3520	64 cc/kilo	2140	1380	39.2	.....	.....	20.0
3-31-47	50 gm.								
	Before Albumin	2550	46.4 cc/kilo	1430	1130	44.3	3.44	46.5	.....
	After Albumin	"3300"		"2170"	"1130"	34.2	.....	.....	.....

NOTE: The figures in quotation marks above are calculations based on an assumption that the RBC volume has remained constant for the period 3-12-47—3-14-47 inclusive. This is a fair assumption since the RBC volume for ten days preceding had remained constant as noted by the figures for these days. Actual blood volume determinations could not be carried out as frequently as desired due to difficulties with vein puncture.

is known in normal individuals who stand after lying down for several hours that the packed cell volume increases and there is a lowered blood volume due to loss of fluid of the blood. We discovered that after giving the albumin for two days the blood volume returned approximately to the previous level. However, at this time the patient was much better subjectively. Then, on the 13th and 14th, we took the packed cell volumes before and after the albumin was given. Using the packed cell volumes, we were able to calculate the blood volume, assuming that the red cell volume was approximately the same during this period of time. On two separate occasions they were actually the same. So, using this figure, we were able to determine the total blood volume. Immediately after the albumin was given the blood volume had increased markedly and was within normal limits. Eighteen to 24 hours later, the blood volume had diminished a thousand cubic centimeters, or 24 per cent of the total. This, apparently, is all in the form of the plasma loss. The determination of total circulating proteins shows that the total circulating proteins increased from 46 grams to 64 grams after 100 grams of albumin were given in two days. At the same time the urinary protein loss, taken for several days previous to giving the albumin and several days after, remained constant. The increase of 18 grams illustrates that about 80 per cent of the albumin had been lost as far as the blood stream is concerned, and that this was not lost in the urine, but was actually metabolized by the patient.

DR. HOPPER: I would like to stress again the relationship of blood volume to the symptoms of dizziness. It was noted that there was a marked drop in blood pressure when the patient raised from a recumbent to the sitting or standing position, accompanied by a feeling of distress. When she stands up, the usual increase in venous pressure found in the legs is exaggerated because the pressure of serum proteins in the circulation is low, and therefore she has a greater tendency to lose fluid with the tissues. Her blood volume drops down to a critical level, and it is no longer possible to maintain blood pressure despite the contraction of the blood vessels.

I am not so sure about this patient's renal function. The low blood volume, I think, makes it pretty difficult to tell, because it is obvious that with the low blood volume she would have a tendency to have glomeruler filtration. So I think that she may have a pre-renal failure but we cannot say this with certainty. Strangely, the nephrotic patient goes to a complete cure better than any of the other chronic glomerulonephritis patient.

Dr. Mudrick has shown you that the albumin given is not reflected by a rise of serum protein. One serum protein value immediately after giving a hundred grams of protein is lower than one at the onset. This simply means that part of the protein is being used in expanding the blood volume. But it looks also as though the protein were going somewhere else, and it is a well known fact that some of these patients go into a positive nitrogen balance for a long time. Some of the protein can undoubtedly go into the tissue stores. One way of looking at it, and much of the experimental work makes this look somewhat correct, is that you have in the body tissues a large reservoir with the serum albumin reflecting the body proteins. Therefore when you put albumin into the circulation it is necessary to raise this whole large reservoir.

Dr. Bennett mentioned to you the patient's failure to eat. When she gets the albumin, she begins to eat much better. But I doubt if she ever gets up to her true caloric needs. Each one gram of albumin is equivalent to four calories, and that albumin, if she isn't getting sufficient calories, is eligible for caloric needs. It is food, so it can be burned to furnish these calories. If one thinks of expense in terms of what one is paying for calories, it really gets very high. Fifty grams a day furnished 200 calories at a cost of $125. I think that shows you why albumin in a certain sense is financially impractical. However, should it save the patient's life, it is highly logical.

I might go back to say a few words about the measurement of blood volume. We are fortunate here in using the carbon monoxide method, and it has an advantage over the dye (Evans Blue) method, particularly in a case like this. In the dye method you introduce the dye into the blood and measure the solution, and it has a fault in that if the serum is cloudy it makes the reading difficult. Secondly, a patient like this almost invariably clears the dye into the urine because it is attached to the protein. Therefore, you get an apparently larger blood volume than the actual blood volume.

DR. STACY R. METTIER:‡ Does the urine output increase after albumin?

DR. HOPPER: It goes up distinctly after giving the albumin.

DR. WILLIAM J. KERR:§ It rises sharply immediately after the albumin but falls off by the next day, correlating with changes in blood volume.

DR. HOPPER: Thorn has maintained patients like this for as long as 30 days. That costs about $3,700. No direct benefit was observed as far as the disease process in the kidney is concerned. However, his patients did get along quite well, during the treatment period had good diuresis, and after the period of therapy were able to maintain a lower weight than previously. The patients had gone into a positive nitrogen balance, which is good. In other words, they stored some nitrogen which was going to carry them along in the future.

DR. T. L. ALTHAUSEN:† Dr. Hopper, one time Epstein gave patients with nephritis large doses of thyroid substance for which he claimed beneficial results. It was mentioned that this patient had milky serum with cholesterol count of 444. It seems to me that is a little low to impart a milky quality to the serum.

DR. HOPPER: The cholesterol is elevated in this patient, but in addition neutral fats, fatty acids and

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phospholipids may be increased and impart a milky appearance to the serum. These patients nearly always have a low basal rate, usually around 30 per cent minus, but they tend to respond as a rule very, very poorly to the administration of thyroid. In some of Epstein's cases, they were given as high as a whole gram per day of thyroid without response. The basal rate didn't go up. One possible explanation of that is that they have such a terrific proteinuria that the particular metabolically active protein is just carried right out. It is obvious that with only 77 grams total circulating protein in the blood, and losing 25 grams a day, every three days all that protein is going to be cleared out and must be replaced by new protein. I do think thyroid is always worth trying in any case. On the other hand, there is another consideration, namely, if you actually increase the metabolic rate of these patients you might tax them in other ways, especially from the point of view of the kidney.

QUESTION: Doctor Hopper, what would be your reaction to the use of gelatine in this patient?

DR. HOPPER: I think that is a pertinent question. Gelatine is undoubtedly much cheaper for one thing. It suffers from the same difficulties that albumin suffers, being cleared out very rapidly. The changes in plasma volume are very transient, lasting only a matter of hours. We have been able to obtain gelatine free of sodium which is of prime importance. Of course gelatine is less physiological than human albumin.

DR. KERR: What do testosterone and some of the other sex hormones do in a patient of this type? Do they tend to cause retention of nitrogen in patients such as this?

DR. HOPPER: Well, testosterone deserves a trial. We have given it to one patient without a spectacular effect. It should be done, and the effect on the total circulating protein should be studied.

I do think, however, along with the general treatment of the patient one should always include a consideration of the kidney lesion, because you may prolong life in many instances if you can keep the patient from going into uremia.

QUESTION: Why couldn't you give whole blood transfusions to build serum proteins?

DR. HOPPER: In this patient you would run into trouble because the patient already has a hemoglobin between 117 per cent and 105 per cent. You would be likely to build up the cells and you might produce vascular accidents, perhaps thrombosis, due to overthick blood.

QUESTION: How does the use of albumin compare with the use of plasma?

DR. HOPPER: They are both costly. I guess the albumin is a little bit more expensive. One trouble is the salt. One would be in difficulty very quickly unless one obtained salt free plasma.